## REMARKS

***Status of the Application***

Claims 22, 43-46 and 48-52 are pending. Claim 22 was previously withdrawn from consideration. Claims 43-46 and 48-52 are currently under examination. Claims 43, 44, 46 and 52 are amended herein. Claim 52 has been amended to remove dependency from claim 43. Support for the amendments can be found throughout the specification and claims as originally filed, for example on page 5, paragraph [0047] (see U.S. Publication No. US 2006/01335556) and originally filed claim 47. No new matter has been added.

***Priority***

In response to Examiner's request, Applicants submit herewith, a copy of priority document PCT/US02/26816 (filed 8/23/2002).

***Allowable Subject Matter***

Applicants thank the Examiner for indicating that claim 52 is allowable.

***Election/Restriction***

The Office Action states that the Restriction Requirement dated August 19, 2008 is made Final. Pursuant to 37 C.F.R. §1.142, on September 8, 2008, Applicants elected Group II, *i.e.* "Claims 1-5, 7, 9-11, 13, 15, 17, 19, 21-25 drawn to compounds of Formula (I), thieno[3,2-d] pyrimidines and simple compositions thereof" in response to this Restriction Requirement. In this response, Applicants repeat their reservation of rights in accordance with the provisions of MPEP §821.04 to rejoin Group IV claims with the elected Group II product claims after an allowable set of claims has been indicated by the Examiner. Applicants also reserve the right to amend the scope of the Group IV claims to be commensurate in scope with the allowed Group II claims. Applicants respectfully assert that rejoinder of the non-elected method claims once compound claims have been allowed is proper as searching claims for methods of using compounds would not add to the Examiner's burden when a search has already been performed for the compounds.

Applicants reserve the right pursuant to 35 U.S.C. § 121 to file one or more continuing applications, such as a divisional, continuation or continuation-in-part, directed to non-elected inventions.

***Rejection under 35 U.S.C. § 102(b) - Soliman***

Applicants acknowledge withdrawal of the rejection of claims 43-45 under 35 U.S.C. § 102(b) as being anticipated by Soliman.

***Rejection under 35 U.S.C. § 102(b) - Shrimali***

Claims 43, 50 and 51 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated over Shrimali *et al* (J. Indian Chem. Soc., 68(8), pp. 466-9, 1991). Specifically, the Examiner states that the "Shrimali ... [C]ompounds 6i, 6k and 6t, read on the compounds of the claimed invention wherein the substituted aryl is *phenyl* ...". As amended, claim 43 reads:

> "... wherein HET is a disubstituted 1,2,4-triazole or a disubstituted imidazole, wherein at least one substituent of the 1,2,4-triazole or imidazole is a substituted aryl that is covalently bound to a nitrogen of the 1,2,4-triazole or imidazole;
> selected from the group consisting of a monosubstituted naphthyl, a disubstituted naphthyl, a trisubstituted naphthyl, a monosubstituted quinoline, a disubstituted quinoline, a trisubstituted quinoline, a monosubstituted isoquinoline, a disubstituted isoquinoline, and a trisubstituted isoquinoline; ..."

Applicants submit that Shrimali does not disclose compounds where the substituted aryl is a monosubstituted naphthyl, a disubstituted naphthyl, a trisubstituted naphthyl, a monosubstituted quinoline, a disubstituted quinoline, a trisubstituted quinoline, a monosubstituted isoquinoline, a disubstituted isoquinoline, or a trisubstituted isoquinoline. Therefore, withdrawal of this rejection is respectfully requested.

***Rejection under 35 U.S.C. § 102(e) - Simoneau***

Claims 43-46 and 48-51 stand rejected under 35 U.S.C. § 102(e) as allegedly being unpatentable over Simoneau *et al* (US 2005/0054639). Simoneau has a publication date of March 10, 2005, and claims priority to a provisional application filed on December 4, 2002. With the submission herewith of priority document PCT/US02/26816, filed August 23, 2002, Applicants have

perfected a priority date for the present application that is prior to that of Simoneau. Applicants submit that Simoneau cannot be used as 103(e) art against the subject application and respectfully request that the rejection be withdrawn.

***Double Patenting***

Claims 43-46 and 48-51 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-19 of U. S. Patent No. 7,435,752. Without conceding to the appropriateness of this rejection, Applicants submit a terminal disclaimer.

Claims 43-46 and 48-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 55 and 83 of copending Application No. 11/661,079 and claims 55 and 83 of copending Application No. 12/114,467. Without conceding to the appropriateness of these rejections, Applicant will consider submitting a terminal disclaimer once allowable subject matter is indicated.

## CONCLUSION

Applicants submit that this response fully addresses the Office Action mailed February 17, 2009 and that for the reasons set forth herein, the pending claims are in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (858) 350-2319.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: June 17, 2009

By: Aubrey Haddach

Aubrey Haddach
Reg. No. 48374

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. **021971**

P2 1120751

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

February 24, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *PCT/US02/26816*
FILING DATE: *August 23, 2002*
RELATED PCT APPLICATION NUMBER: *PCT/US03/27433*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. LAWRENCE
Certifying Officer

# TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

| | |
|---|---|
| Date | DT17 Rec'd PCT/PTO 04 OCT 2002 |
| International Application No. | PCT/US02/26816 |
| Attorney Docket No. | 100848.0217PCT |

**I. Certification under 37 CFR 1.10 (if applicable)**

| EV 099381024 US | |
|---|---|
| Express Mail mailing number | Date of Deposit |

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

| | Collene Houston |
|---|---|
| Signature of person mailing correspondence | Typed or printed name of person mailing correspondence |

**II. ☐ New International Application**

| TITLE | NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS | Earliest priority date (Day/Month/Year) |
|---|---|---|

**SCREENING DISCLOSURE, INFORMATION:** In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign tramnittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was **not** made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)*

| | | | |
|---|---|---|---|
| application no. | | filed on | |
| application no. | | filed on | |

D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages ____ and ☐ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

**III. ☒ A Response to an Invitation from the RO/US.** The following document(s) is(are) enclosed:

A. ☐ A Request for An Extension of Time to File a Response

B. ☒ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

| | | | | | |
|---|---|---|---|---|---|
| pages | | of the request (PCT/RO/101) | pages | | of the figures |
| pages | | of the description | pages | | of the abstract |
| pages | | of the claims | | | |

D. ☐ Submission of Priority Documents

| Priority document | | Priority document | |
|---|---|---|---|

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

**IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette**

**V. ☐ Other** (please specify):

The person signing this form is the:

| | |
|---|---|
| ☐ Applicant | Robert D. Fish |
| ☒ Attorney/Agent (Reg. No.) 33,880 | Typed name of signer |
| ☐ Common Representative | Signature |

**PCT REQUEST**

100848.0217P

Original (for SUBMISSION) - printed on 23.08.2002 04:59:32 PM

| | | |
|---|---|---|
| 0 | For receiving Office use only | |
| 0-1 | International Application No. | PCT/US02/26816 |
| 0-2 | International Filing Date | 23 AUG 2002 (23.08.02) |
| 0-3 | Name of receiving Office and "PCT International Application" | PCT INTERNATIONAL APPLICATION RO/US |
| 0-4 | Form - PCT/RO/101 PCT Request | |
| 0-4-1 | Prepared using | PCT-EASY Version 2.92 (updated 01.06.2002) |
| 0-5 | Petition<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| 0-6 | Receiving Office (specified by the applicant) | United States Patent and Trademark Office (USPTO) (RO/US) |
| 0-7 | Applicant's or agent's file reference | 100848.0217P |
| I | Title of invention | NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS |
| II | Applicant | |
| II-1 | This person is: | applicant only |
| II-2 | Applicant for | all designated States except US |
| II-4 | Name | RIBAPHARM INC. |
| II-5 | Address: | 3300 Hyland Avenue<br>Costa Mesa, CA 92626<br>United States of America |
| II-6 | State of nationality | US |
| II-7 | State of residence | US |
| II-8 | Telephone No. | 714-427-6236 |
| II-9 | Facsimile No. | 714-668-3108 |
| III-1 | Applicant and/or inventor | |
| III-1-1 | This person is: | applicant and inventor |
| III-1-2 | Applicant for | US only |
| III-1-4 | Name (LAST, First) | GIRARDET, Jean-Luc |
| III-1-5 | Address: | 17 Open View Lane<br>Aliso Viejo, CA 92656<br>United States of America |
| III-1-6 | State of nationality | FR |
| III-1-7 | State of residence | US |

PCT REQUEST

100848.0217P

Original (for SUBMISSION) - printed on 23.08.2002 04:59:32 PM

| | | |
|---|---|---|
| III-2 | Applicant and/or Inventor | |
| III-2-1 | This person is: | applicant and inventor |
| III-2-2 | Applicant for | US only |
| III-2-4 | Name (LAST, First) | ZHANG, Zhijun |
| III-2-5 | Address: | 1022 Amber Lynn Court<br>Harbor City, CA 90710<br>United States of America |
| III-2-6 | State of nationality | CN |
| III-2-7 | State of residence | US |
| III-3 | Applicant and/or Inventor | |
| III-3-1 | This person is: | applicant and inventor |
| III-3-2 | Applicant for | US only |
| III-3-4 | Name (LAST, First) | XU, Wen |
| III-3-5 | Address: | 2 McClintock Ct.<br>Irvine, CA 92612<br>United States of America |
| III-3-6 | State of nationality | CN |
| III-3-7 | State of residence | US |
| III-4 | Applicant and/or Inventor | |
| III-4-1 | This person is: | applicant and inventor |
| III-4-2 | Applicant for | US only |
| III-4-4 | Name (LAST, First) | HONG, Zhi |
| III-4-5 | Address: | 79 Timberland<br>Aliso Viejo, CA 92656<br>United States of America |
| III-4-6 | State of nationality | US |
| III-4-7 | State of residence | US |
| III-5 | Applicant and/or Inventor | |
| III-5-1 | This person is: | applicant and inventor |
| III-5-2 | Applicant for | US only |
| III-5-4 | Name (LAST, First) | HAMATAKE, Robert |
| III-5-5 | Address: | 24 Silkwood<br>Aliso Viejo, CA 92656<br>United States of America |
| III-5-6 | State of nationality | US |
| III-5-7 | State of residence | US |

| | | |
|---|---|---|
| IV-1 | Agent or common representative; or address for correspondence<br>The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent |
| IV-1-1 | Name | RUTAN & TUCKER, LLP |
| IV-1-2 | Address: | P.O. Box 1950<br>611 Anton Blvd.<br>Costa Mesa, CA 92628-1950<br>United States of America |
| IV-1-3 | Telephone No. | 714-641-5100 |
| IV-1-4 | Facsimile No. | 714-546-9035 |
| IV-2 | Additional agent(s) | additional agent(s) with same address as first named agent |
| IV-2-1 | Name(s) | FISH, Robert(33,880); ZOETEWEY, David(45,258); THOMPSON, Sandra(46,264); FESSENMAIER, Martin(46,697) |
| V | Designation of States | |
| V-1 | Regional Patent<br>(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT<br>EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT<br>EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT<br>OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT |
| V-2 | National Patent<br>(other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ (patent and utility model) DE (patent and utility model) DK (patent and utility model) DM DZ EC EE (patent and utility model) ES FI (patent and utility model) GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK (patent and utility model) SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW |

**PCT REQUEST**

100848.0217P

Original (for **SUBMISSION**) - printed on 23.08.2002 04:59:32 PM

| | | | |
|---|---|---|---|
| V-5 | **Precautionary Designation Statement**<br>In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. | | |
| V-6 | **Exclusion(s) from precautionary designations** | NONE | |
| VI | **Priority claim** | NONE | |
| VII-1 | **International Searching Authority Chosen** | United States Patent and Trademark Office (USPTO) (ISA/US) | |
| VIII | **Declarations** | Number of declarations | |
| VIII-1 | Declaration as to the identity of the inventor | - | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | - | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - | |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | - | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - | |
| IX | **Check list** | number of sheets | electronic file(s) attached |
| IX-1 | Request (including declaration sheets) | 5 | - |
| IX-2 | Description | 31 | - |
| IX-3 | Claims | 7 | - |
| IX-4 | Abstract | 1 | EZABST00.TXT |
| IX-5 | Drawings | 0 | - |
| IX-7 | TOTAL | 44 | |
| | **Accompanying items** | paper document(s) attached | electronic file(s) attached |
| IX-8 | Fee calculation sheet | ✓ | - |
| IX-17 | PCT-EASY diskette | - | Diskette |
| IX-19 | **Figure of the drawings which should accompany the abstract** | | |
| IX-20 | **Language of filing of the international application** | English | |

**PCT REQUEST**

100848.0217P

Original (for SUBMISSION) - printed on 23.08.2002 04:59:32 PM

| | | |
|---|---|---|
| X-1 | Signature of applicant, agent or common representative | |
| X-1-1 | Name (LAST, First) | FISH, Robert |

**FOR RECEIVING OFFICE USE ONLY**

| | | |
|---|---|---|
| 10-1 | Date of actual receipt of the purported international application | 0703 Rec'd PCT/PTO 23 AUG 2002 (23.08.02) |
| 10-2 | Drawings: | |
| 10-2-1 | Received | |
| 10-2-2 | Not received | |
| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
| 10-4 | Date of timely receipt of the required corrections under PCT Article 11(2) | |
| 10-5 | International Searching Authority | ISA/US |
| 10-6 | Transmittal of search copy delayed until search fee is paid | |

**FOR INTERNATIONAL BUREAU USE ONLY**

| | | |
|---|---|---|
| 11-1 | Date of receipt of the record copy by the International Bureau | |

# PCT

## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s):
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RIBAPHARM INC
3300 Hyland Avenue
Costa Mesa, CA 92626
USA

hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

**Name and address**
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FISH, Robert D.; ZOETEWEY, David J.; THOMPSON, Sandra Poteat; FESSENMAIER, Martin
RUTAN & TUCKER, LLP
P.O. Box 1950
Costa Mesa, CA 92628-1950
USA

to represent the undersigned before

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

USPTO as receiving Office

and to make or receive payments on behalf of the undersigned.

**Signatures of the applicant(s)** *(where there are several persons, each or them must sign next to the signature indicate the name of the person signing and the capacity in which the person signs if such capacity is not obvious from reading this power)*

LOOMIS, Roger; Senior Vice President, Law

Date _____

PCT/US 02/26816

# PCT

## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s):
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GIRARDET, Jean-Luc
RIBAPHARM INC.
3300 Hyland Avenue
Costa Mesa, CA 92626
USA

hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

**Name and address**
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FISH, Robert D.; ZOETEWEY, David J.; THOMPSON, Sandra Poteat; FESSENMAIER, Martin
RUTAN & TUCKER, LLP
P.O. Box 1950
Costa Mesa, CA 92628-1950
USA

to represent the undersigned before

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

USPTO as receiving Office

and to make or receive payments on behalf of the undersigned.

**Signatures of the applicant(s)** *(where there are several persons, each of them must sign; next to the signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):*

GIRARDET, Jean-Luc; Inventor/Applicant

Date: September 20, 2001

Form PCT/Model of general power of attorney (for several international applications)(Jul) 1992)

PCT/US 02/26816
RO/US 04 OCT 2002

# PCT

## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s):
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ZHANG, Zhijun
1022 Amber Lynn Court
Harbor City, CA 90710
USA

hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

**Name and address**
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FISH, Robert D.; ZOETEWEY, David J.; THOMPSON, Sandra Poteat; FESSENMAIER, Martin
RUTAN & TUCKER, LLP
P.O. Box 1950
Costa Mesa, CA 92628-1950
USA

to represent the undersigned before

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

USPTO as receiving Office

and to make or receive payments on behalf of the undersigned.

**Signatures of the applicant(s)** *(where there are several persons, each of them must sign; next to the signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):*

ZHANG, Zhijun; Inventor/Applicant

Date: 09-23-2002

Form PCT/Model of general power of attorney (for several international applications)(July 1992)

PCT/US 02/26816
RO/US 04 OCT 2002

# PCT

## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s):
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

XU, Wen
2 McClintock Ct.
Irvine, CA 92612
USA

hereby appoints (appoint) the following person as: [X] agent [ ] common representative

**Name and address**
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FISH, Robert D.; ZOETEWEY, David J.; THOMPSON, Sandra Poteat; FESSENMAIER, Martin
RUTAN & TUCKER, LLP
P.O. Box 1950
Costa Mesa, CA 92628-1950
USA

to represent the undersigned before

[X] all the competent International Authorities
[ ] the International Searching Authority only
[ ] the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

USPTO as receiving Office

and to make or receive payments on behalf of the undersigned.

**Signatures of the applicant(s)** *(where there are several persons, each of them must sign; next to the signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):*

XU, Wen; Inventor/Applicant

Date: 9-23-02

Form PCT/Model of general power of attorney (for several international applications)(July 1992)

PCT/US 02/26816
RO/US 04 OCT 2002

# PCT

## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s)
*(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)*

HONG, ZHI
RIBAPHARM INC.
3300 Hyland Avenue
Costa Mesa, CA 92626
USA

hereby appoints (appoint) the following person as ☒ agent ☐ common representative

**Name and address**
*(Family name followed by given name; for a legal entity full official designation. The address must include postal code and name of country.)*

FISH, Robert D.; ZOETEWEY, David J.; THOMPSON, Sandra Poteat; FESSENMAIER, Martin
RUTAN & TUCKER, LLP
P.O. Box 1950
Costa Mesa, CA 92628-1950
USA

to represent the undersigned before

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

USPTO as receiving Office

and to make or receive payments on behalf of the undersigned

**Signatures of the applicant(s)** *(where there are several persons, each of them must sign, next to the signature indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power)*

HONG, Zhi; Inventor/Applicant

Date Aug. 28, 2002

Form PCT/Model of general power of attorney (for several international applications)(July 1992)

PCT/US 02/26816
RO/US 04 OCT 2002

# PCT

## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s):
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HAMATAKE, Robert
24 Silkwood
Aliso Viejo, CA 92656
USA

hereby appoints (appoint) the following person as: [X] agent [ ] common representative

**Name and address**
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FISH, Robert D.; ZOETEWEY, David J.; THOMPSON, Sandra Poteat; FESSENMAIER, Martin
RUTAN & TUCKER, LLP
P.O. Box 1950
Costa Mesa, CA 92628-1950
USA

to represent the undersigned before

[X] all the competent International Authorities
[ ] the International Searching Authority only
[ ] the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

USPTO as receiving Office

and to make or receive payments on behalf of the undersigned.

**Signatures of the applicant(s)** *(where there are several persons, each of them must sign; next to the signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):*

HAMATAKE, Robert; Inventor/Applicant

Date: Robert Hamatake 9/23/02

Form PCT/Model of general power of attorney (for several international applications)(July 1992)

**PCT (ANNEX - FEE CALCULATION SHEET)** 100848.0217P

Original (for SUBMISSION) - printed on 23.08.2002 04:59:32 PM

(This sheet is not part of and does not count as a sheet of the international application)

| | | |
|---|---|---|
| 0 | For receiving Office use only | |
| 0-1 | International Application No. | PCT/US02/26816 |
| 0-2 | Date stamp of the receiving Office | 23 AUG 2002 (23.08.02) |

| | | | | | |
|---|---|---|---|---|---|
| 0-4 | Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet | | | | |
| 0-4-1 | Prepared using | PCT-EASY Version 2.92 (updated 01.06.2002) | | | |
| 0-9 | Applicant's or agent's file reference | 100848.0217P | | | |
| 2 | Applicant | RIBAPHARM INC., et al. | | | |
| 12 | Calculation of prescribed fees | | fee amount/multiplier | Total amounts (USD) | |
| 12-1 | Transmittal fee | T | ⇨ | 240 | 240.00 |
| 12-2-1 | Search fee | S | ⇨ | 700 | 700.00 |
| 12-2-2 | International search to be carried out by | | US | | |
| 12-3 | International fee | | | | |
| | Basic fee | | | | 407.00 |
| | (first 30 sheets) | b1 | 407 | | |
| 12-4 | Remaining sheets | | 14 | | 126.00 |
| 12-5 | Additional amount | (X) | 9 | | 446.00 |
| 12-6 | Total additional amount | b2 | 126 | | 1913.00 |
| 12-7 | b1 + b2 = | B | 533 | | -125.00 |
| 12-8 | Designation fees | | | | 1,788.00 |
| | Number of designations contained in international application | | 94 | | |
| 12-9 | Number of designation fees payable (maximum 5) | | 5 | | |
| 12-10 | Amount of designation fee | (X) | 88 | | |
| 12-11 | Total designation fees | D | 440 | | |
| 12-12 | PCT-EASY fee reduction | R | -125 | | |
| 12-13 | Total international fee (B+D-R) | I | ⇨ | 848 | |
| 12-17 | TOTAL FEES PAYABLE (T+S+I+P) | | ⇨ | 1,788 | |
| 12-19 | Mode of payment | | cheque | | |
| 12-20 | Deposit account instructions | | | | |
| | The receiving Office: | | United States Patent and Trademark Office (USPTO) (RO/US) | | |
| 12-20-2 | Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. | | ✓ | | |
| 12-20-3 | Authorization to charge the fee for priority document. | | ✓ | | |
| 12-21 | Deposit account No. | | 502191 | | |
| 12-22 | Date | | 23 August 2002 (23.08.2002) | | |

PCT (ANNEX - FEE CALCULATION SHEET)

100848.0217P

Original (for SUBMISSION) - printed on 23.08.2002 04:59:32 PM

| | | |
|---|---|---|
| 12-23 | Name and signature | FISH, Robert |

VALIDATION LOG AND REMARKS

| | | |
|---|---|---|
| 13-2-4 | Validation messages<br>Priority | Green?<br>No priority of an earlier application has been claimed. Please verify |
| 13-2-7 | Validation messages<br>Contents | Yellow!<br>The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form. |
| | | Green?<br>The international application contains no drawings. Please verify. |
| 13-2-8 | Validation messages<br>Fees | Green?<br>Please confirm that fee schedule utilized is the latest available |

# NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

## Field of The Invention

The field of the invention is enzyme inhibition, and particularly *in vitro* and *in vivo* inhibition of reverse transcriptases.

## Background of The Invention

Numerous treatments for HIV are known in the art, and among other pharmaceutically active compounds, reverse transcriptase inhibitors have provided significant therapeutic effect to many HIV infected patients. For example, Lamivudine (3TC) or Zidovudine (AZT) are relatively well tolerated antiretroviral drugs. However, numerous viral strains have recently emerged with marked resistance against these compounds. To overcome resistance to at least some degree, new nucleoside-type inhibitors may be administered (alone or in combination with other nucleoside-type inhibitors), and exemplary alternative drugs include Stavudine (d4T), Didanosine (ddI), Combivir (a combination of Lamivudine and Zidovudine), and Trizivir (a combination of 3TC, AZT, and Abacavir).

Unfortunately, development of resistance against one nucleoside-type inhibitor may also be accompanied by resistance (to at least some degree) against another nucleoside-type inhibitor, frequently necessitating a switch to a different class of pharmaceutically active molecules. In such cases, a patient may receive a protease inhibitor (*e.g.*, sequinavir, indinavir, nelfinavir, etc.), typically in combination with other anti retroviral agents. However, the relatively complex administration regimen of such combinations often proves an organizational and financial challenge to many patients, and compliance is frequently less than desirable.

In a somewhat better tolerated combination therapy, nucleoside-type inhibitors may be combined with non-nucleoside-type inhibitors. Non-nucleoside-type inhibitors (*e.g.*, Nevirapine, Delavirdine, Efavirenz) are a structurally, relatively inhomogeneous group of compounds and are thought to bind in a non-nucleoside pocket of the reverse transcriptase, thereby significantly increasing antiviral efficacy where nucleoside-type inhibitors is employed. While use of non-nucleoside-type inhibitors seems to provide a promising new class of antiviral drugs, several disadvantages still remain. For example,

the cost for currently known non-nucleoside-type inhibitors is relatively high, and a single mutation in the viral reverse transcriptase can induce a cross resistance against a wide class of non-nucleoside reverse transcriptase inhibitors. Moreover, there is only a limited number of non-nucleoside-type inhibitors available for treatment of an HIV infected patient.

Thus, although various compositions and methods for inhibition of reverse transcriptase, and especially reverse transcriptase from HIV are known in the art, all or almost all of them have one or more disadvantages. Moreover, the HIV virus has a relatively high frequency of mutation, which often leads to drug resistance to current treatments. Therefore, there is still a need to provide new compositions and methods for inhibition of reverse transcriptases.

**Summary of the Invention**

The present invention is directed to methods and compositions for inhibition of a reverse transcriptase wherein various carbonyl amide compounds act as inhibitory compounds of a reverse transcriptase.

In one aspect of the inventive subject matter, a method of inhibiting a reverse transcriptase will include a step in which the reverse transcriptase is presented with a compound having the structure HET-L-C(Y)$NR_1R_2$, wherein HET comprises a heterocycle, L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to H, and wherein another one of the two atoms is covalently bound to the carbonyl atom, Y is oxygen, sulfur, or NH, $R_1$ is selected from the group consisting of hydrogen, halogen, and methyl, or $R_1$ forms a ring with $R_2$ via a chain of between 1-5 atoms; and $R_2$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

In particularly preferred methods, HET is a substituted triazole, and it is even more preferred that the substituted triazole is substituted with a first substituent (*e.g.*, methyl) and a second substituent (*e.g.*, toluyl), wherein at least one of the first and second substituents includes a phenyl group. Moreover, it is generally preferred that L is -$X_1$-$CR_3R_4$-, wherein $X_1$ is selected from the group consisting of S, O, S(O), $S(O)_2$, and $CR_3R_4$; and wherein $R_3$ and $R_4$ are independently hydrogen, halogen, lower alkyl, lower

cycloalkyl, lower alkenyl, lower alkynyl, $NH_2$, OH, and SH. In still further preferred aspects, L is selected from the group consisting of $-S-CH_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, $-O-CH_2-$, and $-CH_2-CH_2-$, and/or Y is O. In still further preferred compounds of such methods, $R_1$ is hydrogen and $R_2$ is a substituted aryl, and more preferably $R_2$ comprises an ortho-substituted phenyl in which the substituent is a halogen or methyl.

Especially contemplated methods include those in which the reverse transcriptase is an HIV reverse transcriptase, and most preferably in which the HIV reverse transcriptase is resistant to a non-nucleoside analog reverse transcriptase inhibitor. Contemplated methods may be performed *in vivo* and/or *in vitro*, and may further include a step in which a compound is converted to a prodrug, and/or a step in which the reverse transcriptase is presented with a second inhibitor (*e.g.*, non-nucleoside reverse transcriptase inhibitor and a nucleoside reverse transcriptase inhibitor).

Therefore, it is contemplated that a method of treating an HIV infected patient may comprise a step in which a pharmaceutical composition comprising a compound according to Structure I is administered to a patient at a dosage effective to reduce viral propagation, wherein Structure I is HET-L-C(Y)$NR_1R_2$, and wherein HET comprises a heterocycle, L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to H, and wherein another one of the two atoms is covalently bound to the carbonyl atom, Y is oxygen, sulfur, or NH, $R_1$ is selected from the group consisting of hydrogen, halogen, and methyl, or $R_1$ forms a ring with $R_2$ via a chain of between 1-5 atoms, and $R_2$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle. With respect to particularly preferred substituents, the same considerations as described above apply.

Consequently, it is contemplated that a pharmaceutical composition will include a compound of the structure HET-L-C(Y)$NR_1R_2$ (with substituents as described above) wherein the compound is present in a concentration effective to inhibit a reverse transcriptase in a cell of a patient when administered to the patient.

In still further contemplated aspects of the inventive subject matter, a compound has a general structure of HET-W-C($R_1$)($R_2$)-C(Y)-N($R_4R_5$), wherein HET comprises a nitrogen-containing heterocycle, W is O, S(O), $S(O)_2$, or $CH_2$, $R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower cycloalkyl, lower alkenyl, lower alkynyl,

halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$, Y is O, S, or $NR_3$, wherein $R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, or hydroxy, O-alkyl, or $CH_2OH$, $R_4$ is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl, or $R_4$ forms a ring with $R_5$ via a chain of between 1-5 atoms, and $R_5$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

In yet another aspect of the inventive subject matter, a compound has a general structure of HET-S-C($R_1$)($R_2$)-C(Y)-N($R_4R_5$), wherein HET comprises a nitrogen-containing heterocycle, $R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower cycloalkyl, lower alkenyl, lower alkynyl, halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$, and with the proviso that $R_1$ and $R_2$ are not hydrogen at the same time, Y is O, S, or $NR_3$, wherein $R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, or hydroxy, O-alkyl, or $CH_2OH$, $R_4$ is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl, or $R_4$ forms a ring with $R_5$ via a chain of between 1-5 atoms, and $R_5$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

In still other aspects of the inventive subject matter, a compound has a general structure of HET-W-C($R_1$)($R_2$)-C(Y)-N($R_4R_5$), wherein HET comprises a nitrogen-containing heterocycle other than a triazole, W is O, S, S(O), $S(O)_2$, or $CH_2$, $R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$, Y is O, S, or $NR_3$, wherein $R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, or hydroxy, O-alkyl, or $CH_2OH$, $R_4$ is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl, or $R_4$ forms a ring with $R_5$ via a chain of between 1-5 atoms, and $R_5$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention, along with the accompanying drawings in which like numerals represent like components.

**Detailed Description**

The inventors surprisingly discovered that a reverse transcriptase, and particularly the reverse transcriptase of HIV may be inhibited by numerous compounds that include a

carbonyl amide moiety. Consequently, methods and compositions are contemplated that inhibit a reverse transcriptase *in vitro* and *in vivo*. Further especially contemplated methods include methods of treatment of a patient infected with HIV, and particularly contemplated compositions include selected carbonyl amide compounds and pharmacological compositions thereof.

As used herein, the term "halogen" refers to a fluorine, bromine, chlorine, or iodine, which is typically covalently bound to another atom (e.g., carbon). As further used herein, the term "hydroxyl" refers to a –OH group. As still further used herein, the term "carbonyl atom" refers to a carbon atom to which three atoms are covalently bound, wherein one of the three atoms is bound to the carbon atom via a double bond (which may be partially delocalized). Thus, particularly contemplated carbonyl atoms include carbon atoms in a carboxamide group, a carboxamidine group, and a thiocarboxamide group.

The term "alkyl" as used herein refers to a cyclic, branched, or straight hydrocarbon in which all of the carbon-carbon bonds are single bonds, and the term "lower alkyl" refers to a cyclic, branched, or straight chain alkyl of one to ten carbon atoms (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), cyclopropylmethyl, i-amyl, n-amyl, hexyl, etc.). The term "cycloalkyl" as used herein refers to a cyclic or polycyclic alkyl group containing 3 to 15 carbons. For polycyclic groups, these may be multiple condensed rings in which one of the distal rings may be aromatic (*e.g.*, indanyl, tetrahydronaphthalene, etc.).

Similarly, the term "alkenyl" as used herein refers to an alkyl in which at least one carbon-carbon bond is a double bond. Thus, the term "lower alkenyl" includes all alkenyls with one to ten carbon atoms. The term "cycloalkenyl" as used herein refers to a cyclic or polycyclic group containing 3 to 15 carbons and at least one double bond. Likewise, the term "alkynyl" as used herein refers to an alkyl or alkenyl in which at least one carbon-carbon bond is a triple bond. Thus, the term "lower alkynyl" includes all alkynyls with one to ten carbon atoms.

As still further used herein, the term "alkoxy" refers to a –OR group, wherein R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or

substituted cycloheteroalkyl. Similarly, the term "aryloxy" refers to a –OAr group, wherein Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group.

Furthermore, the terms "aryl" and "Ar" are used interchangeably herein and refer to an aromatic carbocyclic group having at least one aromatic ring (*e.g.*, phenyl or biphenyl) or multiple condensed rings in which at least one ring is aromatic, (*e.g.*, 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl). Similarly, the terms "heterocycle" or "heterocyclic ring" are used interchangeably herein and refer to a saturated, partially or entirely unsaturated, or aromatic carbocyclic group having a single ring (*e.g.*, morpholino, pyridyl or furyl) or multiple condensed rings (*e.g.*, naphthpyridyl, quinoxalyl, quinolinyl, or indolizinyl) which include at least one heteroatom within the ring(s). The term "heteroatom" as used herein refers to an atom other than carbon (*e.g.*, S, O, or N), which can optionally be substituted with, e.g., hydrogen, halogen, lower alkyl, alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like. Thus, the term "heteroaryl" refers to a heterocycle in which at least one heterocyclic ring is aromatic.

Still further, the term "substituted" as used herein means that a hydrogen atom that is covalently bound to a group or atom (or a free electron pair or electron pair of a double bond of an atom) is replaced by a covalently bound non-hydrogen substituent, including hydroxyl, thiol, alkylthiol, halogen, alkoxy, amino, amido, nitro, carboxyl, cycloalkyl, heterocycle, cycloheteroalkyl; acyl, carboxyl, aryl, aryloxy, heteroaryl, arylalkyl, heteroarylalkyl, alkyl, alkenyl, alknyl, and cyano.

The term "prodrug" as used herein refers to a modification of contemplated compounds, wherein the modified compound exhibits less pharmacological activity (as compared to the unmodified compound) and wherein the modified compound is converted within a target cell (*e.g.*, T-cell) or target organ (*e.g.*, lymph node) back into the unmodified form. For example, conversion of contemplated compounds into prodrugs may be useful where the active drug is too toxic for safe systemic administration, or where the contemplated compound is poorly absorbed by the digestive tract, or where the body breaks down the contemplated compound before reaching its target.

As further used herein, the term "inhibiting a reverse transcriptase" refers to a reduction of the formation of DNA from a template RNA or DNA by a reverse transcriptase, wherein the reduction may be directly or indirectly achieved in various manners. For example, direct inhibition includes suicide, competitive and non-competitive inhibition, allosteric inhibition, or binding of an inhibitor in a non-nucleoside pocket. Examples on indirect inhibition include depletion of nucleosides for DNA synthesis, induction or contribution to conformational changes, etc.

As still further used herein, the term "reducing [or: to reduce] viral propagation" means that the titer of a virus in a sample is lowered, wherein the reduction may include various manners, including partial or total inhibition of viral replication, partial or total inhibition of protein processing or assembly, viral exit of an infected cell, and/or clearance of the virus from a system via immune response to the virus.

**Contemplated Compounds**

The inventors generally contemplate that all compounds of formula (I) are suitable for use herein:

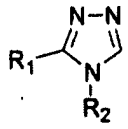
$$HET\text{-}L\text{-}C(Y)NR_1R_2 \quad (I)$$

wherein HET comprises a heterocycle; L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom; Y is O, S, or $NR_3$; $R_1$ and $R_3$ are independently selected from the group consisting of hydrogen, halogen, and lower alkyl; and $R_2$ is selected from the group consisting of an aryl, a cycloalkyl, a cycloalkenyl, and a heterocycle.

With respect to the heterocycle it is preferred that at least one, and more typically at least two of the heteroatoms are nitrogen, and that the two heteroatoms are connected to each other in the heterocycle via a covalent bond. Consequently, particularly suitable heterocycles include a triazole (most preferably a 1,2,4-triazole) ring system. In alternative aspects, however, suitable heterocycles may also include 4-, 5-, and 6-membered rings with at least one heteroatom (*e.g.*, O, N, or S), wherein such rings may further be coupled or fused to at least one other ring (which may or may not include a heteroatom).

Particularly preferred heterocycles include at least one, and even more preferably at least two substituents, wherein suitable substituents independently include a substituted and/or an unsubstituted aryl, a substituted and/or an unsubstituted alkyl, a substituted and/or an unsubstituted alkenyl, a substituted and/or an unsubstituted alkynyl, wherein each of the two substituents may further include one or more heteroatoms. However, especially preferred heterocycles will include a lower alkyl (and most preferably a methyl or trifluoromethyl) as one substituent and a substituted or unsubstituted phenyl (*e.g.*, halogenated or toluyl) as the other substituent.

Consequently, particularly preferred heterocycles will have a structure according to formula (II)




(II)

wherein $R_1$ and $R_2$ are independently hydrogen, halogen, lower alkyl, cycloalkyl, alkenyl, alkynyl, aryl (all of which may be substituted), OH, SH, $NO_2$, $NR_1R_2$ (with $R_1$ and $R_2$ as defined above), $N_3$, and/or an O-alkyl.

In further contemplated aspects, it should be recognized that the structure and chemical nature of suitable linkers may vary substantially. For example, where it is desired that the linker has a relatively rigid character (*i.e.*, at least one, and more typically two degrees of rotational freedom are restricted), suitable linkers may include a double and/or triple bond, or include atoms in a planar configuration (e.g., aromatic or carbonyl structure). On the other hand, where the linker may have flexibility to at least some degree, suitable linkers may include an alkyl group or an oxygen or sulfur atom. Thus, suitable linkers may include various heteroatoms, and particularly preferred heteroatoms are oxygen and sulfur (in various oxidation states).

Consequently, contemplated linkers include particularly those in which at least two atoms form a contiguous chain (via a covalent bond), wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is

covalently bound to the carbonyl atom of contemplated compounds. Thus, particularly preferred linkers will have a structure according to formula (III)

$$-X_1-CR_3R_4- \quad \text{(III)}$$

wherein $X_1$ is a heteroatom, and most preferably S, S(O), $S(O)_2$, O. Alternatively, $X_1$ may also include a carbon atom and may thus have the structure $-(CR_5R_6)_n-$ wherein n is between 1 and five, and wherein $R_3$, $R_4$, $R_5$, and $R_6$ are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, $NH_2$, OH, and/or SH. Therefore, suitable linkers will include those having the structure $-S-CH_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, $-O-CH_2-$, and $-CH_2-CH_2-$.

Moreover, it should be appreciated that the carbonyl carbon may be covalently bound to various atoms/groups, and particularly suitable groups include O (to form a carboxamide), S (to form a thiocarboxamide), and NR (to form a carboxamidine), wherein R may be hydrogen, or a substituted or unsubstituted lower alkyl. Suitable alternative R include all those that will provide a hydrogen bond donor or acceptor group. Consequently, Y of formula (I) may be O, S, or NR, with R as defined above.

Similarly, the nature of the substituents of the nitrogen atom that is covalently bound to the carbonyl carbon may vary considerably, and all known substituents of secondary amines are contemplated herein. Therefore, $R_1$ and $R_2$ in formula (I) may be independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, all of which may further include one or more heteroatoms. However, it is generally preferred that one of $R_1$ and $R_2$ is relatively small (*e.g.*, hydrogen, methyl, trifluoromethyl, etc.), while the other of $R_1$ and $R_2$ comprises an aryl group. Especially preferred aryl groups will be substituted, most preferably in ortho-position, and may further include a substituent in para-position (*e.g.*, ortho-substituted phenyl with halogen or methyl as substituent). Therefore, especially contemplated $R_1$ will include a hydrogen and lower alkyl (which may be further substituted), while $R_2$ may be selected from the group consisting of an aryl, a cycloalkyl, a cycloalkenyl, and a heterocycle.

In an especially preferred aspect, the heterocycle is covalently bound to the linker via a group other than -S-, and the linker has a relatively short and relatively flexible

structure of -W-C($R_1$)($R_2$)-. Consequently, contemplated compounds will have a structure according to formula (IV)

HET-W-C($R_1$)($R_2$)-C(Y)-N($R_4R_5$) (IV)

wherein HET is defined as in formula (I) above, and wherein C(Y)-N($R_4R_5$) is defined as C(Y)N$R_1R_2$ in formula (I) above. With respect to W, it is generally contemplated that all groups other than –S- are appropriate, and particularly preferred groups include O, S(O), $S(O)_2$, and $CH_2$. Particularly preferred $R_1$ and $R_2$ and relatively small radicals, and it is especially preferred that $R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$.

Alternatively, where it is desired that the heterocycle is covalently bound to the linker via a –S- group, and where the linker is relatively short and flexible, contemplated compounds may have a structure according to formula (V)

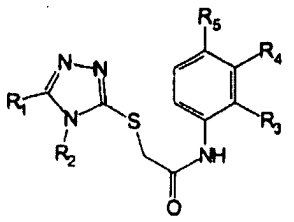
HET-S-C($R_1$)($R_2$)-C(Y)-N($R_4R_5$) (V)

in which HET, $R_1$, $R_2$, Y, $R_4$ and $R_5$ are defined as above, with the proviso that that $R_1$ and $R_2$ are not hydrogen at the same time.

In a still further contemplated aspect of the inventive subject matter, and especially where the heterocyclic base is a nitrogen-containing heterocycle other than a triazole, suitable compounds may have a structure according to formula (VI)

HET-W-C($R_1$)($R_2$)-C(Y)-N($R_4R_5$) (VI)

wherein HET comprises a nitrogen-containing heterocycle other than a triazole, wherein W is O, S, S(O), $S(O)_2$, or $CH_2$, and wherein $R_1$, $R_2$, $R_4$, and $R_5$ are defined as described above in formula (V) above. Thus, particularly preferred compounds will have a structure according to Formula A



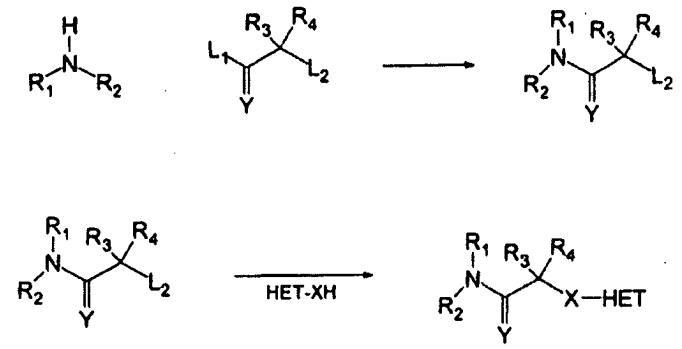
(A)

wherein $R_1$, $R_4$, and $R_5$ are independently lower alkyl or hydrogen, $R_2$ is cycloalkyl, substituted aryl, or unsubstituted aryl, and $R_3$ is lower alkyl or halogen.

**Synthesis of Contemplated Compounds**

It should be particularly appreciated that some of the contemplated compounds are commercially available from various sources, and all of the commercially available compounds are contemplated suitable for use herein. However, numerous of the contemplated compounds are not commercially available, and synthesis of such compounds may proceed according to a protocol substantially as described in U.S. Pat. No. 5,939,462, which is incorporated by reference herein.

In one exemplary synthetic route, a suitably substituted amine (*e.g.*, primary or secondary amine) is reacted with an activated carbonyl containing compound (preferably a carbonyl halide), wherein the carbonyl containing compound further includes a leaving group (and most preferably bromine). After formation of the carbonyl amide, the reaction product is reacted with a nucleophilic group (*e.g.*, OH, SH, or $NR_1R_2$ with $R_1$ and $R_2$ independently hydrogen alkyl, etc.) of a second reagent thereby replacing the leaving group to form the desired compound as depicted in Scheme 1 below.




*Scheme 1*

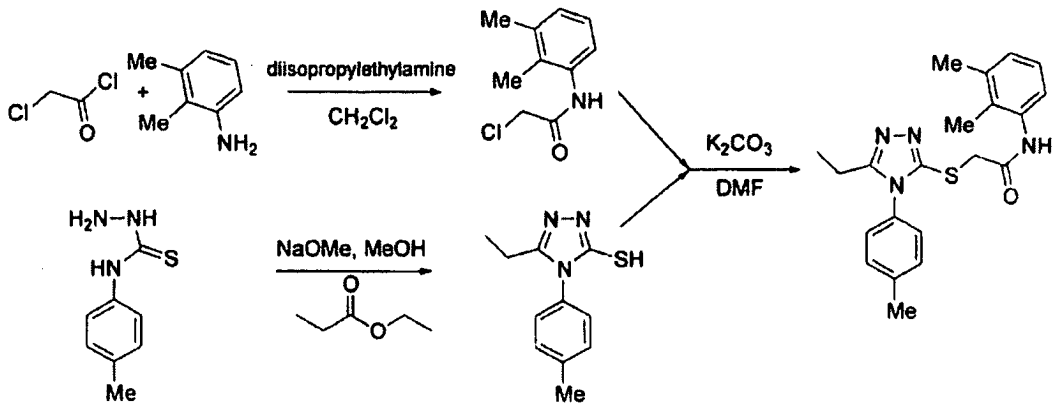
$R_1$ and $R_2$ of Scheme 1 may be any suitable substituent and is generally contemplated that appropriate $R_1$ and $R_2$ independently include hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, all of which may further include one or more heteroatoms. However, it is generally preferred that one of $R_1$ and $R_2$ is relatively small (*e.g.*, hydrogen, methyl, trifluoromethyl, etc.), while the other of $R_1$ and $R_2$ comprises an aryl group. Especially preferred aryl groups will be substituted, most preferably in ortho-position, and may further include a substituent in para-position (*e.g.*, ortho-substituted phenyl with halogen or methyl as substituent). Therefore, especially contemplated $R_1$ will include a hydrogen and lower alkyl (which may be further substituted), while $R_2$ may be selected from the group consisting of an aryl, a cycloalkyl, a cycloalkenyl, and a heterocycle.

Similarly, it is contemplated that the choice of leaving groups $L_1$ and $L_2$ will depend at least to some extent up on the particular choice of the amine and/or HET-XH, and all suitable leaving groups are contemplated. However, it is particularly preferred that $L_1$ and $L_2$ are a halide, and most preferably a bromide. Alternatively, $L_1$ may also be OH or O-Acyl. With respect to $R_3$ and $R_4$ the same considerations as described above for $R_3$ and $R_4$ in formula (III). Likewise, X is a heteroatom or $CH_2$, and most preferably S, S(O), $S(O)_2$, O, and Y may be O, S, or NR with R as defined above. Likewise, HET may be any heterocycle, and particularly suitable heterocylces include those described above.

Suitable solvents include ethers, alcohols, and hydrocarbons (optionally halogenated) and the choice of suitable solvents will at least in part depend on the

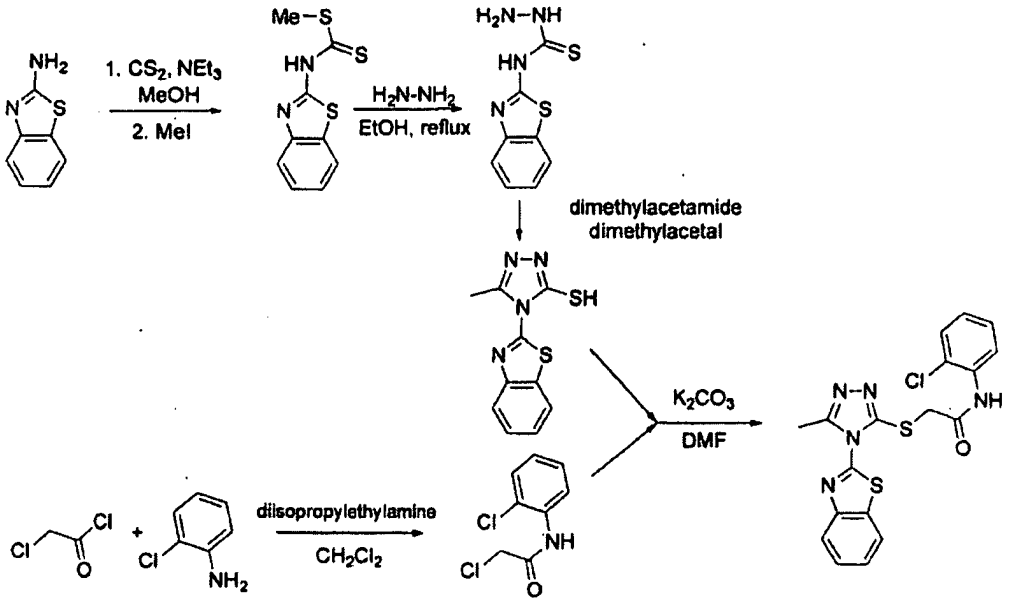
chemical nature of the particular reagent. Furthermore with respect to the catalyst and/or base employed in the above reaction, the same considerations as those described by Connell et al. (.S. Pat. No. 5,939,462) apply.

Alternatively, synthesis may follow a general protocol as outlined in Scheme 2, in which contemplated compounds are prepared from two previously prepared precursors. The first precursor comprising a substituted heterocycle is prepared following a protocol substantially similar to the protocol given below in the section entitled "Examples". Similarly, the second precursor comprising the substituted aryl is prepared following a protocol substantially similar to the protocol given below in the section entitled "Examples", and fusion of the previously prepared precursors is typically carried out in DMF with potassium carbonate.




*Scheme 2*

Where the substituted heterocycle is substituted with a heteroaryl or an aryl for which the corresponding thiosemicarbizide is not commercially available and the aryl comprises an ortho-substituted chlorophenyl. a synthetic procedure as described in Scheme 3 below may be employed which substantially follows similar procedures as the protocol given below in the section entitled "Examples".




*Scheme 3*

In still further contemplated aspects, and especially where contemplated compounds include an acid or a basic group, it should be appreciated that the corresponding salt (and preferably a pharmacologically acceptable salt) may be formed. For example, where contemplated compounds include a basic group, an acid addition salt may be prepared. Acid addition salts of such basic compounds can be prepared in a standard manner in a suitable solvent from the compound and an excess of acid, including hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or methanesulfonic acid. Likewise, if contemplated compounds include an acidic group, alkaline addition salts may be prepared (e.g., by treatment of the acidic compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing an appropriate cation. Suitable cations include $Na^+$, $K^+$, $Ca^{2+}$, or $NH_4^+$).

**Pharmaceutical Compositions comprising Contemplated Compound**

Where contemplated compounds are administered in a pharmacological composition, it is contemplated that suitable compounds can be formulated in admixture with a pharmaceutically acceptable carrier. For example, contemplated compounds can be administered orally as pharmacologically acceptable salts (see above), or intravenously in

physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated compounds may be modified to render them more soluble in water or another vehicle, which for example, may be easily accomplished by minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

In certain pharmaceutical dosage forms, prodrug forms of contemplated compounds may be formed for various purposes, including reduction of toxicity, increasing the organ- or target cell specificity, etc. One of ordinary skill in the art will recognize how to readily modify the present compounds to pro-drug forms to facilitate delivery of active compounds to a target site within the host organism or patient (see above). One of ordinary skill in the art will also take advantage of favorable pharmacokinetic parameters of the pro-drug forms, where applicable, in delivering the present compounds to a targeted site within the host organism or patient to maximize the intended effect of the compound.

In addition, contemplated compounds may be administered alone or in combination with other agents for the treatment of HIV, and particularly contemplated additional compounds include nucleoside-type reverse transcriptase inhibitors (*e.g.*, Lamivudine, Zidovudine, Stavudine, Abacavir, Tenofovir or Didanosine ), non-nucleoside reverse transcriptase inhibitors (*e.g.*, Nevirapine, Delavirdine, Efavirenz), protease inhibitors (*e.g.*, Sequinavir, Indinavir, Nelfinavir), a fusion inhibitor (*e.g.*, T20), a CCR5 antagonist, immunotherapeutic agents (*e.g.*, ribavirin, IL-2), and/or a therapeutic vaccine. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative

timings of administration will be selected in order to achieve the desired combined therapeutic effect.

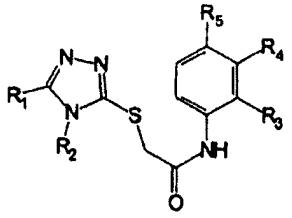
Therefore, the inventors contemplate that a pharmaceutical composition may comprise a compound of structure HET-L-C(Y)$NR_1R_2$, wherein HET comprises a heterocycle, L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom, Y is O, S, or $NR_3$, $R_1$ and $R_3$ are independently selected from the group consisting of hydrogen, halogen, and lower alkyl, $R_2$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle, and wherein the compound is present in a concentration effective to inhibit a reverse transcriptase and/or HIV replication in a cell of a patient when administered to the patient.

With respect to suitable concentrations of contemplated compounds in pharmaceutical compositions, it should be appreciated that a person of ordinary skill in the art will readily adjust the amount of the compound to achieve inhibition of the reverse transcriptase and/or HIV replication. For example, inhibition of the HIV replication in a cell (typically a T-cell infected with the HIV virus) may be monitored *in vitro* using a blood culture and a luciferase based assay system as described below. Alternatively, inhibition of the reverse transcriptase may be monitored *in vivo* using RT-PCR to determine the amount of copies of viral DNA and/or RNA in blood or lymph nodes (containing HIV infected cells). However, it is generally contemplated that suitable concentrations will achieve a serum concentration of between 1 nM (in some cases even between 0.01 nM and 1 nM) and 100 microM.

In particularly preferred compounds, HET is a substituted triazole, and it is even more preferred that the substituted triazole is substituted with a first substituent (*e.g.*, methyl) and a second substituent (*e.g.*, toluyl) , and wherein at least one of the first and second substituents includes a phenyl group. Furthermore, it is generally preferred that the linker L has the structure -$X_1$-$CR_3R_4$-, wherein $X_1$ is selected from the group consisting of $CH_2$, S, O, S(O), $S(O)_2$, and $CR_3R_4$, and wherein $R_3$ and $R_4$ are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, $NH_2$, OH, and SH. Thus, especially preferred linkers include those in which L is –S-$CH_2$-, -S(O)-$CH_2$-, –$S(O)_2$-$CH_2$-,

–O-$CH_2$-, or -$CH_2$-$CH_2$-. Moreover, particularly suitable substituents for the nitrogen atom $R_1$ and $R_2$ include hydrogen and a substituted aryl, respectively, and an especially preferred R2 is an ortho-substituted phenyl (wherein the ortho-substituent is a halogen or a methyl).

Consequently, particularly preferred pharmaceutical compositions will include contemplated compounds according to Structure A below:




(A)

wherein $R_1$, $R_4$, and $R_5$ are independently lower alkyl or hydrogen, $R_2$ is cycloalkyl, substituted aryl, or unsubstituted aryl, and $R_3$ is lower alkyl or halogen.

**Contemplated Methods of Use**

The inventors surprisingly discovered (for experiments and data see below in the section with the title "Examples") that contemplated compounds exhibit significant *in vitro* and/or *in vivo* inhibitory effect on a reverse transcriptase, and especially on the reverse transcriptase of the HIV virus.

Consequently, the inventors contemplate a method of inhibiting a reverse transcriptase in which a reverse transcriptase is presented with a compound according to structure (I)

HET-L-C(Y)$NR_1R_2$ (I)

wherein HET comprises a heterocycle; L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom; Y is O, S, or $NR_3$; $R_1$ and $R_3$ are independently selected from the group consisting of hydrogen,

halogen, and lower alkyl; and $R_2$ is selected from the group consisting of an aryl, a cycloalkyl, a cycloalkenyl, and a heterocycle.

In particularly preferred aspects of contemplated methods, the heterocycle comprises a nitrogen-containing heterocycle, and is most preferably substituted triazole. While the substituent or substituents on contemplated heterocycles may vary considerably, it is generally preferred that the substituted triazole will include a first and second substituent, wherein the first substituent is relatively small (*e.g.*, methyl, trifluoromethyl, nitro, amino, hydroxy, or thio group) and wherein the second substituent includes an aromatic system (and most preferably a phenyl or toluyl). With respect to the aromatic system, the inventors discovered that where the aromatic system comprises a phenyl group, particularly strong inhibition could be achieved where the phenyl group has a substituent in the ortho-position.

Furthermore, it is contemplated that the nature and particular structure of the linker connecting the heterocycle to the carbonyl carbon may vary considerably, and it is generally contemplated that the linker may allow steric flexibility or may orient the heterocycle in a relatively fixed position relative to the carbonyl group. For example, where the linker is relatively flexible, it is contemplated that all of covalent bonds between the atoms that form a contiguous chain to connect the heterocycle with the carbonyl carbon are single bonds. Of course, it should be recognized that the bond angle between such atoms will depend at least to some degree on the chemical nature of the atoms. Therefore, relatively straight angles (*e.g.*, where the atom is O or S) are contemplated as well as non-straight angles (*e.g.*, where the atom is C or P).

On the other hand, where the linker is relatively rigid, suitable linkers may include two or more atoms (within the contiguous chain of atoms that connect the heterocycle with the carbonyl carbon) that are covalently coupled to each other via a double or triple bond. Such linkers may therefore include unsaturated straight or branched hydrocarbons chains, or aromatic rings. Alternatively, contemplated linkers may also include cycloalkyl groups. Moreover, suitable linkers may further include various functional groups to provide particular physicochemical properties, including a hydrogen bond donor or acceptor group, a polar or non-polar group, an ionic group, or a lipophilic group. Thus, suitable

linkers may include between 2 and 20 (and even more) atoms, which may or may not include heteroatoms.

Consequently, particularly preferred linkers may have the structure $-X_1-CR_3R_4-$, wherein $X_1$ is selected from the group consisting of S, O, S(O), $S(O)_2$, and $CR_3R_4$, and wherein $R_3$ and $R_4$ are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, $NH_2$, OH, and SH. Even more preferred linkers will include those selected from the group of $-S-CH_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, $-O-CH_2-$, and $-CH_2-CH_2-$.

In yet further aspects of preferred methods, the carbonyl carbon may be covalently bound to an oxygen, sulfur, or an NH or NR group, wherein R may be selected from the group consisting of hydrogen, halogen, and lower alkyl. Consequently, contemplated compounds may include a carboxamide group, a (substituted) carboxamidine group, or a thiocarboxamide group.

In still further aspects of preferred methods, $R_1$ and $R_2$ may vary considerably, and all $R_1$ and $R_2$ groups contemplated above in the section entitled "Contemplated Compounds" are considered suitable for use herein. However, it is generally preferred that $R_1$ is hydrogen and $R_2$ is a substituted aryl (and most preferably that $R_2$ comprises an ortho-substituted phenyl, wherein the ortho-substituent is a halogen or a methyl).

It should further be appreciated that contemplated methods of inhibition of a reverse transcriptase need not be limited to a particular reverse transcriptase, and it should be recognized that all known reverse transcriptases are considered suitable for use herein. However, it is particularly preferred that the reverse transcriptase is a viral reverse transcriptase, and in especially preferred aspects the viral reverse transcriptase is from HIV. Moreover, the inventors discovered that such reverse transcriptases may be inhibited even when the reverse transcriptase is at least partially resistant to a non-nucleoside analog reverse transcriptase inhibitor. The term "at least partially resistant to a non-nucleoside analog reverse transcriptase inhibitor" as used herein means that the 'at least partially resistant' reverse transcriptase is inhibited by previously known non-nucleoside reverse transcriptase inhibitors to a lesser degree than a non-resistant reverse transcriptase (see section with the title "Examples").

With respect to the step of presenting the reverse transcriptase, it is contemplated that all manners of presentation are suitable and include numerous *in vitro* and *in vivo* presentations. For example, where presentation of the reverse transcriptase with contemplated compounds is *in vitro*, it should be appreciated that the reverse transcriptase may be in a solvent or supported on a solid phase (and optionally in the presence of an RNA or DNA template, cofactors, and nucleosides, etc.). Contemplated solvents include those that are predefined (*e.g.*, reverse transcriptase buffer) as well as those where the exact chemical composition is highly complex (*e.g.*, cell lysate). Suitable solid phases include gels, polymer beads, walls of a microplate, etc. Furthermore, particularly contemplated *in vitro* presentation also includes a presentation where the reverse transcriptase is enclosed by a cell (infected by the HIV virus, or transfected and transformed to produce recombinant reverse transcriptase).

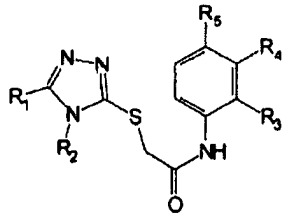
Thus, *in vitro* presentation includes all manners of presentation in which the reverse transcriptase is in the same environment as contemplated compounds. Consequently, contemplated compounds may be added to a buffer, medium, or other solvent in which the reverse transcriptase is present, and addition of contemplated compounds includes addition in dissolved form as well as in solid form. With respect to the particular form (*e.g.*, as solution in a particular solvent) in which contemplated compounds are added to the environment, a person of ordinary skill in the art will readily determine a suitable form. Similarly, the appropriate concentration may readily be determined by a person of ordinary skill in the art without undue experimentation (*e.g.*, using $IC_{50}$ data as guidance).

Similarly, contemplated *in vivo* presentations include all manners of adding contemplated compounds in a suitable formulation to an environment that contains the reverse transcriptase, and especially contemplated environments include mammals infected with a retrovirus, and most preferably the HIV virus. Consequently, particularly preferred *in vivo* presentations include administration of pharmaceutical compositions comprising contemplated compounds to a patient that is infected with the HIV virus. Thus, suitable administration may be oral and/or parenteral (systemic) administration as well as ex vivo administration to whole blood or components thereof with reintroduction of at least a portion of the whole blood or components thereof. Exemplary pharmaceutical

compositions are described above in the section with the title "Pharmaceutical Compositions comprising Contemplated Compound".

Therefore, the inventors contemplate a method of treating an HIV infected patient in which a pharmaceutical composition comprising a compound according to Structure I is administered to the patient at a dosage effective to reduce viral propagation, wherein Structure I is HET-L-C(Y)$NR_1R_2$, in which HET comprises a heterocycle, L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom, Y is oxygen, sulfur, NH, or NR (with R as described above), $R_1$ is selected from the group consisting of hydrogen, halogen, and methyl, and $R_2$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle. With respect to particularly preferred structures, the same considerations as described above in the section entitled "Contemplated Compounds" apply.

Therefore, particularly preferred compounds for treatment of an HIV infected patient include those in which HET is a substituted triazole, and/or L is selected from the group consisting of $-S-CH_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, $-O-CH_2-$, and $-CH_2-CH_2-$, and in which Y is oxygen. In still further preferred compounds for treatment methods, $R_1$ is hydrogen and $R_2$ is a substituted aryl. Thus, particularly preferred compounds for treatment of an HIV infection include compounds of structure A:




(A)

wherein $R_1$, $R_4$, and $R_5$ are independently lower alkyl or hydrogen, $R_2$ is cycloalkyl, substituted aryl, or unsubstituted aryl, and $R_3$ is lower alkyl or halogen. With respect to the dosage, it is contemplated that the dosage will predominantly depend on the particular compound employed (*e.g.*, particular solubility, efficacy, bioavailability and/or metabolic

profile), and it should be recognized that a person of ordinary skill in the art will readily be able to determine the proper dosage or dosage range. Similarly, reduction of viral propagation may be monitored using various methods well known in the art. For example, viral propagation may be measured using quantitative RT-PCR to determine the number of viral copies in a particular biological sample (e.g., whole blood).

Of course, it should be recognized that, where desirable, contemplated compounds may be converted into a prodrug form to increase specificity towards an infected cell, to reduce adverse activity in non-infected cells, to increase bioavailability, etc., and suitable administration formulations, routes, and protocols are well known in the art (see also above).

**Examples**

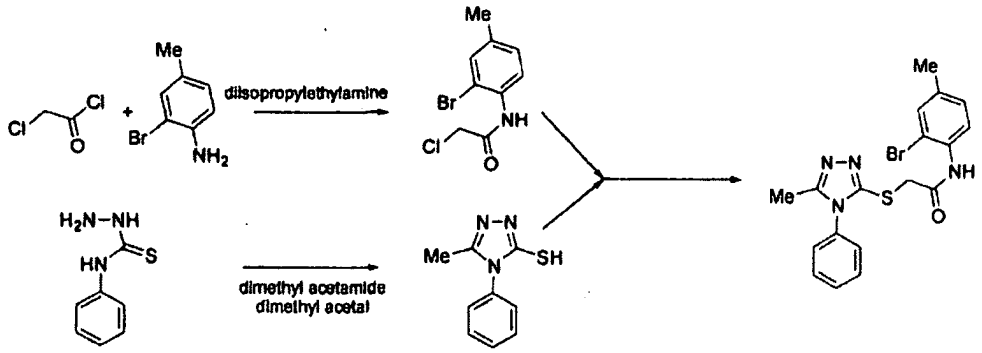
The following experiments are provided only to illustrate exemplary aspects of the inventive subject matter and should not be understood as limiting the inventive subject matter.

*N-(2-Bromo-4-methylphenyl)-2-(5-methyl-4-phenyl-4H-[1,2,4]triazole-3-ylsulfanyl)acetamide (Scheme 2)*

A mixture of 5-Methyl-4-phenyl-4H-1,2,4-triazole-3-thiol (200 mg, 1.05 mmol), potassium carbonate (153.6 mg, 1.1 mmol), and N-(2-Bromo-4-methylphenyl)-2-chloroacetamide (273.5 mg, 1.05 mmol) in N,N-dimethylformamide (5 mL) was stirred overnight. The resulting mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium chloride solution, and dried over $MgSO_4$. Removal of the solvent in vacuo and flash chromatography of the residue afforded the desired compound.

Preparation of N-(2-Bromo-4-methylphenyl)-2-chloroacetamide: 2-Bromo-4-methylphenyl (500 mg, 2.69 mmol) was added to a mixture of chloroacetylchloride (0.14 mL, 2.69 mmol) and diisopropylmethylamine (0.47 mL, 2.69 mmol) in dichloromethane (16 mL). After 4 hours of stirring, the mixture was diluted with ethyl acetate and washed with 1 N hydrochloric acid, water, saturated aqueous sodium chloride solution, and dried over $MgSO_4$. Removal of the solvent in vacuo afforded the desired compound.

Preparation of 5-Methyl-4-phenyl-4H-1,2,4-triazole-3-thiol: A suspension of 4-phenyl-3-thiosemicarbazide (10 g, 59.8 mmol) in dimethyl acetamide dimethyl acetal (30 mL, 205 mmol) was heated in an open flask on a steam bath for 1.5 h. Removal of the solvent and flash chromatography of the residue (2% methanol/dichloromethane) afforded a mixture of 5-methyl-4-phenyl-4H-1,2,4-triazole-3-thiol and 3-methyl-5-methylthio-4-phenyl-4H-1,2,4-triazole.




*Scheme 2*

*Test System for Determination of Inhibition of HIV-1 Reverse Transcriptase*

Contemplated compounds were screened for inhibitory activity against human immunodeficiency virus type 1 (HIV-1) using a high throughput cell-based assay using HIV-1 expressing firefly luciferase as a reporter gene and pseudotyped with vesicular stomatitis virus envelope glycoprotein (VSV-G). Experimental procedures were essentially as described by Connor et al. in *Journal of Virology* (1996), 70: 5306-5311 (Characterization of the functional properties of *env* genes from long-term survivors of human immunodeficiency virus type 1 infection), and Popik et al. in *Journal of Virology* (2002), 76: 4709-4722 (Human immunodeficiency virus type 1 uses lipid raft-colocalized CD4 and chemokine receptors for productive entry into $CD4^+$ T cells). It should be particularly appreciated that the virus contains two introduced mutations in the RT gene (K103N and Y181C, created by PCR mutagenesis) that render the virus highly resistant to current non-nucleoside HIV-1 drugs. Virus stocks were generated by co-transfection of plasmid DNA encoding VSV-G with vector pNL4-3Env(-)Luc(+) into 293T cells. Sixty-four hours after transfection, virus-containing medium was collected by centrifugation and stored frozen at –80° C.

HeLa cells were infected with the VSV-G pseudotyped virus in the presence of screening compounds in a 384-well microtiter plate format. Forty-eight hours after initial infection, lysis buffer and Luciferase Assay Reagent (Promega) was added to the cells and luciferase activity was determined by counting the resultant luminescence using a LJL luminometer. Since the luciferase gene is carried in the virus genome, its expression level directly reflects the virus replication level in the presence of a compound.

To evaluate the activity of the compounds against wild type HIV-1, the HeLa-JC53 cell line that expresses high levels of CD4 and CCR5 (see *e.g.*, Platt et al. in *Journal of Virology* (1998), 72: 2855-2864: Effect of CCR5 and CD4 cell surface concentrations on infection by macrophagetropic isolates of human immunodeficiency virus type 1) was modified by isolation of a stable cell line that expresses luciferase under the control of the HIV-1 promoter (long terminal repeat, *i.e.*, LTR). HIV-1 infection of this cell line stimulates the transcription of luciferase from the HIV-1 promoter and the luciferase gene expression level is proportional to the level of virus replication (Harrington et al. in *Journal of Virology Methods* (2000), 88: 111-115: Direct detection of infection of HIV-1 in blood using a centrifugation-indicator cell assay; and Roos et al. in *Virology* (2000), 273: 307-315: LuSIV cells: a reporter cell line for the detection and quantitation of a single cycle of HIV and SIV replication). Procedures for virus infection, compound testing and luciferase activity determination were the same as for the VSV-G pseudotyped HIV-1.

Two approaches were used to evaluate the cytotoxicity of the positive compounds discovered in the HIV-1 virus assays. The first approach employed another modified HeLa-JC53 cell line that constitutively expresses high level of luciferase without virus infection. The level of luciferase expression in these cells served as an indicator for cell replication in the presence of the compounds. Procedures for compound testing and luciferase activity determination were the same as for the virus infection tests. The other toxicity assay utilized HeLe-JC53 cells and a commercially available MTS assay kit (Promega) that measures the mitochondria function of the cells.

*Results*

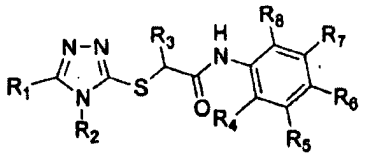
Table 1 below depicts values for inhibitory activity of exemplary compounds. Inhibitory activity is indicated as $EC_{50}$ in microM for HIV, and $IC_{50}$ is indicated in microM for wild-type HIV RT. Inhibitory activity at concentrations of less than 10

microM are labeled A, inhibitory activity at concentrations of between 10 microM to 100 microM are labeled B, and inhibitory activity at concentrations of greater than 100 microM are labeled C.

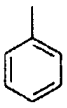
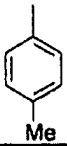
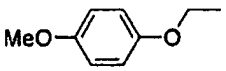
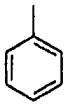
| ID | EC50 | IC50 |
|---|---|---|
| 1 | A | A |
| 2 | A | A |
| 3 | B | A |
| 4 | C | A |
| 5 | C | A |
| 6 | B | A |
| 7 | B | A |
| 8 | B | A |
| 9 | B | A |
| 10 | C | N/D |
| 11 | C | N/D |
| 12 | C | N/D |
| 13 | C | N/D |
| 14 | C | N/D |
| 15 | C | N/D |
| 16 | C | N/D |
| 17 | C | N/D |
| 18 | C | N/D |
| 19 | C | N/D |
| 20 | C | N/D |
| 21 | C | N/D |
| 22 | C | N/D |
| 23 | C | N/D |
| 24 | C | N/D |
| 25 | C | N/D |
| 26 | B | N/D |
| 27 | C | N/D |
| 28 | C | N/D |
| 29 | C | B |
| 30 | C | N/D |
| 31 | C | N/D |
| 32 | C | N/D |
| 33 | C | B |
| 34 | C | B |
| 35 | C | N/D |
| 36 | C | N/D |
| 37 | C | N/D |
| 38 | N/D | B |

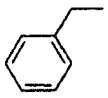
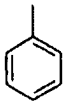
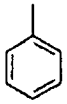
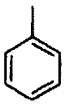
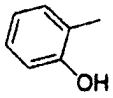
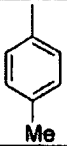
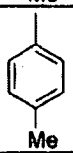
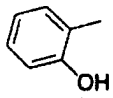
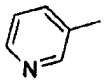
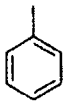
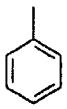
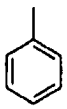
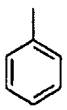
| | | |
|---|---|---|
| 39 | C | N/D |
| 40 | C | B |
| 41 | C | B |
| 42 | C | N/D |
| 43 | C | B |
| 44 | C | B |
| 45 | C | 36.27 |
| 46 | C | C |
| 47 | C | N/D |
| 48 | C | N/D |
| 49 | C | N/D |
| 50 | C | N/D |
| 51 | C | N/D |
| 52 | C | B |

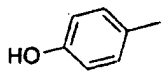
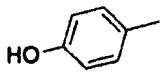
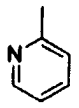
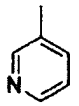
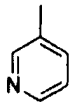
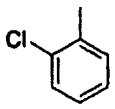
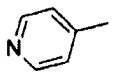
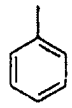
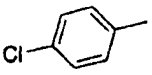
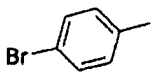
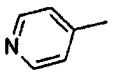
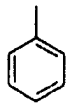
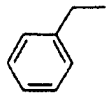
With respect to the particular compounds listed as Compound ID 1-52, Table 2 below depicts the substituents for the respective compounds based on the scaffold as shown above. The structures of compounds with the ID 3, 10, 22, and 25 are depicted below in Table 2.

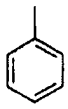
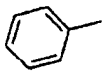
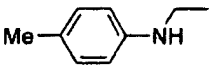
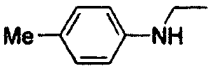
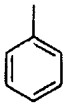
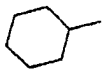
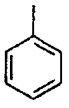
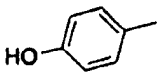
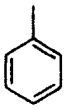
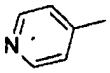
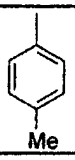
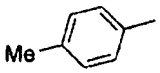
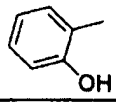
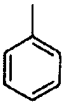
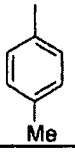
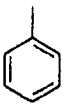


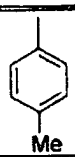
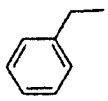
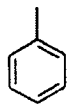
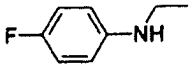
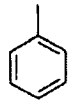
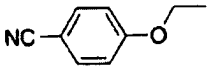
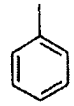
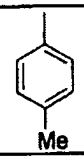
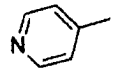
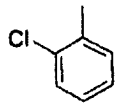
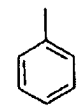
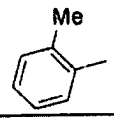
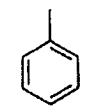
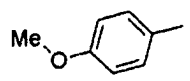
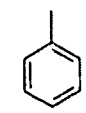

Scaffold for Table 2

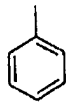
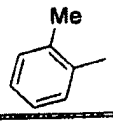
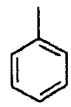
| ID | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ |
|---|---|---|---|---|---|---|---|---|
| 1 | Me |  | H | Br | H | Me | H | H |
| 2 | Me |  | H | Cl | H | H | H | H |
| 4 |  |  | H | Br | H | Me | H | H |

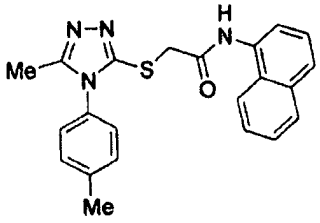
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5 |  |  | H | Br | H | Me | H | H |
| 6 | Me |  | H | Me | H | H | H | H |
| 7 | Me |  | H | Me | H | Me | H | H |
| 8 |  |  | H | Br | H | H | H | H |
| 9 | Me |  | H | Me | Me | H | H | H |
| 11 |  | H | H | H | H | F | H | H |
| 12 |  | Me | H | H | H | Me | H | H |
| 13 | Me |  | H | H | H | $NO_2$ | H | H |
| 14 | Me |  | H | Me | H | H | H | Me |
| 15 | Me |  | H | H | H | F | H | H |
| 16 | Me |  | Me | Me | H | H | H | H |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 17 |  | Me | Me | H | H | Me | H | H |
| 18 |  | Me | H | H | Me | H | Me | H |
| 19 | H |  | H | Br | H | H | H | H |
| 20 | H |  | H | $CF_3$ | H | H | H | H |
| 21 | H |  | H | H | $CF_3$ | Cl | H | H |
| 23 | Me |  | H | $CF_3$ | H | H | H | H |
| 24 |  |  | H | I | H | H | H | H |
| 26 |  | H | H | Me | H | H | H | H |
| 27 |  | Me | H | H | H | H | H | H |
| 28 |  |  | H | Br | H | Me | H | H |
| 29 |  | Me | H | Br | H | Me | H | H |

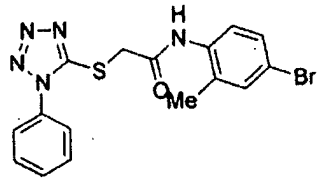
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 30 | Me |  | H | H | Me | Me | H | H |
| 31 |  | Me | H | Br | H | Me | H | H |
| 32 |  | Me | H | Br | H | Me | H | H |
| 33 |  |  | H | Br | H | Me | H | H |
| 34 |  |  | H | Br | H | H | H | H |
| 35 |  |  | H | Br | H | H | H | H |
| 36 |  |  | H | Br | H | Me | H | H |
| 37 |  | Me | H | Br | H | H | H | H |
| 38 |  |  | H | Br | H | H | H | H |
| 39 | Me |  | H | H | Cl | Me | H | H |
| 40 | Me |  | H | H | Me | H | H | H |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 41 | Me |  | H | H | H | C(O)Me | H | H |
| 42 |  |  | H | H | H | Me | H | H |
| 43 |  |  | H | Br | H | Me | H | H |
| 44 |  |  | H | Br | H | Me | H | H |
| 45 | Me |  | Me | H | H | Me | H | H |
| 46 |  |  | H | Br | H | Me | H | H |
| 47 | Me |  | H | H | H | Me | H | H |
| 48 |  | Me | H | Br | H | Me | H | H |
| 49 | Me |  | H | H | H | H | H | H |
| 50 |  |  | H | Br | H | H | H | H |

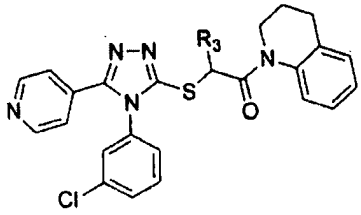
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 51 | Me |  | H | Me | H | Me | H | Me |
| 52 |  |  | H | Br | H | Me | H | H |



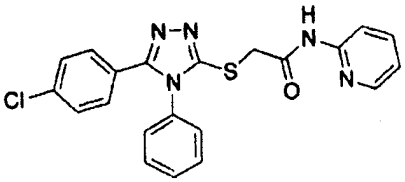
ID 3



ID 10



ID 22



ID 25

Thus, specific embodiments and applications of non-nucleoside reverse transcriptase inhibitors have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

## CLAIMS

What is claimed is:

1. A method of inhibiting a reverse transcriptase, comprising:

presenting the reverse transcriptase with a compound according to Structure I

$$HET\text{-}L\text{-}C(Y)NR_1R_2 \quad (I)$$

wherein HET comprises a heterocycle;

L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom;

Y is O, S, or $NR_3$;

$R_1$ and $R_3$ are independently selected from the group consisting of hydrogen, halogen, and lower alkyl; and

$R_2$ is selected from the group consisting of an aryl, a cycloalkyl, a cycloalkenyl, and a heterocycle.

2. The method of claim 1 wherein HET is a substituted triazole.

3. The method of claim 2 wherein the substituted triazole is substituted with a first substituent and a second substituent, and wherein at least one of the first and second substituents includes a phenyl group.

4. The method of claim 3 wherein the first substituent is methyl and the second substituent is toluyl.

5. The method of claim 1 wherein L is $-X_1-CR_3R_4-$, wherein

$X_1$ is selected from the group consisting of S, O, S(O), $S(O)_2$, and $CR_3R_4$; and

$R_3$ and $R_4$ are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, $NH_2$, OH, and SH.

6. The method of claim 1 wherein L is selected from the group consisting of $-S-CH_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, $-O-CH_2-$, and $-CH_2-CH_2-$.

7. The method of claim 1 wherein Y is O.

8. The method of claim 1 wherein $R_1$ is hydrogen and $R_2$ is a substituted aryl.

9. The method of claim 8 wherein $R_2$ comprises an ortho-substituted phenyl.

10. The method of claim 9 wherein the ortho-substituent is a halogen or a methyl.

11. The method of claim 1 wherein the reverse transcriptase is an HIV reverse transcriptase.

12. The method of claim 11 wherein the HIV reverse transcriptase is at least partially resistant to a non-nucleoside analog reverse transcriptase inhibitor.

13. The method of claim 1 wherein the step of presenting the reverse transcriptase comprises *in vivo* presentation.

14. The method of claim 1 wherein the compound is converted to a prodrug before the step of presenting.

15. The method of claim 1 further comprising presenting the reverse transcriptase with a second inhibitor.

16. The method of claim 15 wherein the second inhibitor is selected from the group of a non-nucleoside reverse transcriptase inhibitor and a nucleoside reverse transcriptase inhibitor.

17. A method of treating an HIV infected patient comprising:

administering to the patient a pharmaceutical composition comprising a compound according to Structure I at a dosage effective to reduce viral propagation;

$$HET\text{-}L\text{-}C(Y)NR_1R_2 \quad (I)$$

wherein HET comprises a heterocycle;

L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom;

Y is oxygen or sulfur;

$R_1$ is selected from the group consisting of hydrogen, halogen, and methyl; and

$R_2$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

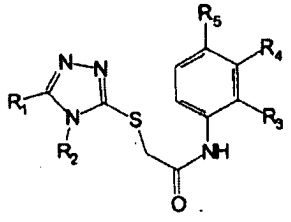
18. The method of claim 17 wherein HET is a substituted triazole.

19. The method of claim 18 wherein L is selected from the group consisting of –S-$CH_2$-, -S(O)-$CH_2$-, –$S(O)_2$-$CH_2$-, –O-$CH_2$-, and -$CH_2$-$CH_2$-.

20. The method of claim 18 wherein Y is O.

21. The method of claim 18 wherein $R_1$ is hydrogen and $R_2$ is a substituted aryl.

22. The method of claim 17 wherein the compound has a structure according to




structure II,

(II)

wherein $R_1$, $R_4$, and $R_5$ are independently lower alkyl or hydrogen, $R_2$ is cycloalkyl, substituted aryl, or unsubstituted aryl, and $R_3$ is lower alkyl or halogen.

23. The method of claim 22 further comprising co-administering a second antiviral medicament.

24. The method of claim 23 wherein the second medicament is selected from the group of a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, a nucleoside reverse transcriptase inhibitor, an integrase inhibitor, a viral binding inhibitor, and a fusion inhibitor.

25. A pharmaceutical composition comprising a compound of structure HET-L-$C(Y)NR_1R_2$, wherein HET comprises a heterocycle, L is a linker in which at least two atoms form a contiguous chain, wherein one of the two atoms is covalently bound to the heterocycle, and wherein another one of the two atoms is covalently bound to the carbonyl atom, Y is O, S, or $NR_3$, $R_1$ and $R_3$ are independently selected from the group consisting of hydrogen, halogen, and lower alkyl, $R_2$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle, and wherein the compound is present in a concentration effective to inhibit a reverse transcriptase in a cell of a patient when administered to the patient.

26. The composition of claim 25 wherein HET is a substituted triazole.

27. The composition of claim 26 wherein the substituted triazole is substituted with a first substituent and a second substituent, and wherein at least one of the first and second substituents includes a phenyl group.

28. The composition of claim 27 wherein the first substituent is methyl and the second substituent is toluyl.

29. The composition of claim 25 wherein L is $-X_1-CR_3R_4-$, wherein

$X_1$ is selected from the group consisting of $CH_2$, S, O, S(O), $S(O)_2$, and $CR_3R_4$; and

$R_3$ and $R_4$ are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, $NH_2$, OH, and SH.

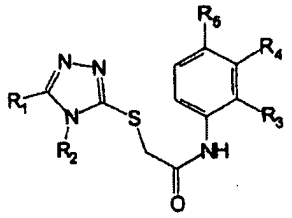
30. The composition of claim 25 wherein L is selected from the group consisting of $-S-CH_2-$, $-S(O)-CH_2-$, $-S(O)_2-CH_2-$, $-O-CH_2-$, and $-CH_2-CH_2-$.

31. The composition of claim 25 wherein $R_1$ is hydrogen and $R_2$ is a substituted aryl.

32. The composition of claim 31 wherein $R_2$ comprises an ortho-substituted phenyl.

33. The composition of claim 32 wherein the ortho-substituent is a halogen or a methyl.

34. The composition of claim 25 wherein the compound has a structure according to structure II,



(II)

wherein $R_1$, $R_4$, and $R_5$ are independently lower alkyl or hydrogen, $R_2$ is cycloalkyl, substituted aryl, or unsubstituted aryl, and $R_3$ is lower alkyl or halogen.

35. A compound having a structure according to structure VII

$$HET\text{-}W\text{-}C(R_1)(R_2)\text{-}C(Y)\text{-}N(R_4R_5) \quad (VII)$$

wherein HET comprises a nitrogen-containing heterocycle;

W is O, S(O), $S(O)_2$, or $CH_2$;

$R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$;

Y is O, S, or $NR_3$, wherein $R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, or hydroxy, O-alkyl, or $CH_2OH$;

$R_4$ is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl; and

$R_5$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

36. The compound of claim 35 wherein HET comprises a triazole.

37. The compound of claim 36 wherein $R_1$, $R_2$, and $R_4$ are hydrogen, and wherein $R_5$ is comprises an ortho-substituted phenyl.

38. The compound of claim 37 wherein Y is O.

39. A compound having a structure according to structure VII

$$HET\text{-}S\text{-}C(R_1)(R_2)\text{-}C(Y)\text{-}N(R_4R_5) \quad (VII)$$

wherein HET comprises a substituted aromatic nitrogen-containing heterocycle;

$R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$, and with the proviso that $R_1$ and $R_2$ are not hydrogen at the same time;

Y is O, S, or $NR_3$, wherein $R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, or hydroxy, O-alkyl, or $CH_2OH$;

$R_4$ is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl; and

$R_5$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

40. The compound of claim 39 wherein HET comprises a triazole.

41. The compound of claim 40 wherein $R_1$, $R_2$, and $R_4$ are hydrogen, and wherein $R_5$ is comprises an ortho-substituted phenyl.

42. The compound of claim 41 wherein Y is O.

43. A compound having a structure according to structure VII

$$HET\text{-}W\text{-}C(R_1)(R_2)\text{-}C(Y)\text{-}N(R_4R_5) \quad (VII)$$

wherein HET comprises a substituted aromatic nitrogen-containing heterocycle other than a triazole;

W is O, S, S(O), $S(O)_2$, or $CH_2$;

$R_1$ and $R_2$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, OH, SH, $NH_2$, $N_3$, O-alkyl, or $CH_2OH$;

Y is O, S, or $NR_3$, wherein $R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, or hydroxy, O-alkyl, or $CH_2OH$;

$R_4$ is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl; and

$R_5$ is selected from the group consisting of an aryl, a cycloalkanyl, a cycloalkenyl, and a heterocycle.

44. The compound of claim 43 wherein HET comprises a triazine.

45. The compound of claim 44 wherein $R_1$, $R_2$, and $R_4$ are hydrogen, and wherein $R_5$ is comprises an ortho-substituted phenyl.

46. The compound of claim 45 wherein Y is O.

## ABSTRACT

Various carbonyl amides are employed *in vitro* and *in vivo* as non-nucleoside inhibitors of a reverse transcriptase, and particularly of HIV reverse transcriptase. Therefore, contemplated compounds may be employed in the treatment of HIV infected patients. Further contemplated aspects include pharmaceutical compositions comprising therapeutically effective amounts of contemplated compounds.